REMARKS

Reconsideration and allowance are respectfully requested.

Claims 6, 8, 9, and 11 are pending. The Examiner has withdrawn claim 11 from consideration as being directed to a non-elected invention. In this response, claims 6 and 8 are amended for clarity. Support for the amendments can be found in the specification and claims as originally filed. For example, the specification in Example 5 discloses a pharmaceutical formulation containing a therapeutically effective amount of insulin. Furthermore, the specification at page 10, lines 11-21 discloses fat cell and receptor binding assays for insulin activity. No new matter is added. Accordingly, claims 6, 8, and 9 are at issue.

Rejections Under 35 U.S.C. § 112, First and Second Paragraphs

Claim 8 has been rejected under 35 U.S.C. § 112, first paragraph, for lack of written description. The Examiner contends that the recitation of "*in vitro* activity" could encompass more than the "hypoglycemic activity described in the specification" (Office Action at page 3.) Claim 8 has also been rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness. The Examiner contends that the claim does not reflect the metes and bounds of the claimed activities. These rejections are respectfully traversed.

The present specification at page 10 clearly discloses the use of fat cell and receptor binding assays to quantify the biological activity of insulin. Accordingly, in this response claim 8 has been amended to reflect this disclosure. On this basis, it is respectfully submitted that these rejections have been overcome and may be withdrawn.

Rejections Under 35 U.S.C. § 102

Claims 6, 8, and 9 have been rejected under 35 U.S.C. § 102(b) as anticipated by Affholter et al., *Biochemistry* 29: 7727 (1990). The Examiner contends that the disclosure of Affholter et al. suggests that insulin analogues can be used to inhibit insulin-degrading enzymes (IDE) and that the article thereby anticipates the presently claimed pharmaceutical formulation. This rejection is respectfully traversed.

The present inventors were the first to identify inactive insulin analogues as suitable agents for immune tolerization against pathological autoimmune syndromes that result in Type I diabetes. Nothing in Affholter et al. discloses or suggests the use of pharmaceutical formulations comprising inactive insulin analogues to treat diabetes. To the contrary, Affholter et al.'s use of Asp-B25 human insulin demonstrated that this analogue exhibited severely reduced binding to both IDE and insulin receptor (see, e.g., discussion at page 7732, first column, third full paragraph.) According to Affholter, these properties would make Asp-B25 insulin unsuitable for therapeutic use as an IDE inhibitor.

Furthermore, even the potential use of insulin analogues as IDE inhibitors as suggested by Affholter et al. is irrelevant to the present invention. Strikingly, Affholter et al. contains not a single indication that any therapeutic use was contemplated for IDE inhibitors. See, e.g., the final sentence of the discussion (at page 7732, second column), which states: "These insights may facilitate the design of protease-resistant insulin analogues and peptide-based inhibitors of insulin-degrading enzyme, *which will be useful in further elucidating the role of IDE in insulin and IGF action*" (emphasis added). Clearly, the disclosure of Affholter et al. relates only to physical chemical experiments involving insulin and insulin analogues and has no relevance to pharmaceutical formulations.

Claims 6, 8, and 9 have also been rejected under 35 U.S.C. § 102(b) as anticipated by Drejer et al., *Diabetes* 40:1488 (1991). The Examiner contends that Drejer et al. disclose compositions comprising Asp-B25 human insulin and suggest that such compositions may be "valuable for *in vitro* and *in vivo* studies", and that such suggestion anticipates the present invention. This rejection is respectfully traversed.

Drejer et al., taken as a whole, is an analysis of receptor binding properties of a group of insulin analogues, including Asp-B25 human insulin (Asp-B25 human insulin is the least active of the group). Similar to Affholter et al., in Drejer et al. there is not a single reference to the possibilities of therapeutic use of any of the analogues. Furthermore, it is respectfully submitted that the Examiner has taken Drejer's words out of context. The last paragraph of Drejer et al. reads: "The availability of analogues with a broad range of receptor affinities may enable us to reach a better understanding of the mechanism of insulin action. In particular, analogues with very low and very high affinities will continue to be valuable for in

vivo and in vitro studies." Seen in context, the last sentence unambiguously refers to experimental studies only, and any possible relevance of Asp-B25 human insulin to such studies is an "outlyer" (i.e., as lying on one extreme of --low-- receptor binding).

Neither Affholter et al. nor Drejer et al. discloses any possible therapeutic use of Asp-B25 human insulin nor of any hormonally inactive insulin analogues. Consequently, neither Affholter et al. nor Drejer et al. discloses pharmaceutic formulations containing effective amounts of such analogues for treating or ameliorating diabetes. On this basis, it is respectfully submitted that neither reference anticipates the presently claimed invention.

In view of the above amendments and remarks, it is believed that the claims are in condition for allowance, and a determination to that effect is earnestly solicited.

Respectfully submitted,

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